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09/736,151	12/15/2000	Ali Laayoun	104959	8406

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EXAMINER

TUNG, JOYCE

ART UNIT	PAPER NUMBER
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1637 14
DATE MAILED: 08/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/736,151

Applicant(s)

Laayoun et al.

Examiner

Joyce Tung

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on May 20, 2003.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-39 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 1, 2, 4-8, 10-15, and 19-39 is/are rejected.

7) Claim(s) 3, 9, and 16-18 is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

4) Interview Summary (PTO-413) Paper No(s). _____

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

6) Other: _____

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DETAILED ACTION

1. The amendment filed 5/20/2003 has been entered. Following the entry of the amendment, claims 1-39 are pending.

Rejections and/or objected from the previous office action are hereby withdrawn. The following rejections are either newly applied or reiterated. They constitute the complete set presently being applied to the instant application.

Double Patenting

- 2 The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1, 19, 22-25, and 33-38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 5, 7, 16, 18-19, 22, 24, and 26-35 of U.S. Patent No. 6/376,179. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims 1, 19, 22-25 and 33-38 are drawn to a method of fragmenting and labeling at least synthetic or natural member selected

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from the group consisting of DNA, RNA and chimeric DNA-RNA polymer in that at least one DNA or RNA comprising one thiophosphate nucleotide. The method of the instant invention comprises chemically fragmentation of the member in the presence of at least one multivalent metal cation to produce a plurality of fragment and attaching at least one label to the fragment with a labeling agent to produce a detectably labeled fragment. Claims 1-2, 5, 7, 16, 18-19, 22, 24, and 26-35 of U.S. Patent No. 6/376,179 are also drawn to a method for labeling a synthetic or natural RNA involving fragmenting the RNA to produce a plurality of RNA fragments having freed terminal phosphates in the presence of metal cation as recited in claims 7, 16 and chemical catalyst as recited in claims 5 and 18 and labeling a plurality of the fragment with labels recited in claims 24, 27-29 and 34-35 at the terminal phosphates freed in the fragmenting step. The differences of two inventions are that the instant method additionally applies to DNA molecule fragmenting and labeling. The RNA molecule and DNA molecule contain the same nucleotide molecules. The method of fragmenting RNA molecules would have been used in fragmenting DNA molecules. Therefore, this is the judicially created doctrine of obviousness-type double patenting rejection.

The response argues that the cited '179 claims limit the claimed subject matter to RNA only and the '179 claims do not teach or suggest instant claims 1. However, the RNA molecule and DNA molecule contain the same nucleotide molecules. The method of fragmenting RNA molecules would have been used in fragmenting DNA molecules. The rejection is maintained.

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Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 4-6, 8, 10-13, 19-20, 23-26, 29 and 32-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morrow (5,684,149) in view of Mirzabekov et al. (5,981,734).

Morrow et al. disclose a method to fragment RNA in the presence of a metal complexes (See the Abstract). The metal complexes can promote the cleavage of RNA (See column 6, lines 34-37) in which typical metals include copper, zinc, cobalt, lead and so on as listed in claims 26 and 32 (See column 6, lines 48-54 and See example I-IV). Morrow et al. indicate that zinc ion in the presence of imidazole buffers has been shown to catalyze the hydrolysis of the RNA dimmer (See column 1, lines 39-42).

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Morrow et al. do not disclose the use of the method for fragmenting DNA. Morrow et al. also do not disclose attaching at least one label to said fragments with a labeling agent to produce a detectably labeled fragment and the concentration of labeling agent used in the method. Additionally, Morrow et al. do not disclose treating said aqueous solution to decrease or eliminate unattached labeling agent.

Mirzabekov et al. disclose a method for labeling oligonucleotide molecules in which fragmented DNA and RNA are labeled with fluorescence dye (See column 5, lines 4-14, 29-31). The amount of Fluorescence dye used is 1ul of 4mM TMR-hydrazine in 10ul of sodium acetate buffer (See column 6, lines 44-46). Mirzabekov et al. also disclose that the butanol extraction from acid aqueous solutions substantially separates the labeled product from the excess of unreacted fluorophore without laborious procedures such as dialysis (See column 7, lines 66-67, column 8, lines 1-2).

Mirzabekov et al. do not specifically indicate separating the labeled nucleic acid fragment from the unattached labeling agent by using solid phase extraction of the nucleic acid fragment on a solid support. However, Mirzabekov et al. disclose a method of immobilizing nucleic acid on solid support, gel substrate (See column 2, lines 39-42 and column 8, lines 11-23). In fact, the labeled nucleic acid would be separated by using immobilization technics and this was also well known technics in the art at the time of the instant invention for separation.

One of ordinary skill in the art would have been motivated to combine the teachings of Morrow et al. and Mirzabekov et al. to carry out the method of fragmenting DNA or RNA in the

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presence of metal ions because the metal complexes are catalytically active and kinetically inert to metal ion dissociation (See the Abstract) and the method of Mirzabekov et al. is an efficient labeling method which is independent of the oligonucleotide length (See column 2, lines .26-28) in which the active center for the attachment of dye is created by modifying the nucleic acid molecule (See column 2, lines 60 and column 3, lines 1-3). In addition, one of ordinary skill in the art would know to adjust the concentration of dye for optimizing the reaction condition to have a reasonable expectation of success. It would have been prima facie obvious to carry out the method as claimed.

The response argues that the reference of Morrow does not disclose a method to fragment DNA. However, DNA molecules and RNA molecules have the same nucleotide molecules. Therefore the method used in fragmenting RNA would have been used in fragmenting RNA. Nevertheless, the limitations of claims 4 and 26 also requires RNA in the method.

The response next argues that Morrow describes metal complexes with catalytic behavior in RNA cleavage by promoting transesterification of the phosphate diester linkage of RNA. However, the limitations of claims 1, 4-6, 8, 10-13, 19-20, 23-26, 29 and 32-37 do not limit to the transesterification of the phosphate diester linkage of RNA for fragmenting DNA or RNA.

The response also argues that the method of Morrow applies the metal complexes to single-stranded RNA. The claim language does not require the RNA molecules or DNA molecules which are single stranded or double stranded. Thus, the argument does not commensurate the scope of the claims.

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The response further argues that Mirzabekov discloses labeling nucleic acids at their terminal ends and that the label is not located at the terminal phosphate, but rather is located (I) for DNA, on the sugar moiety after the base has been eliminated during depurination in an acidic medium (see fig. 1) or (ii) for RNA , at the 2' or 3' position of the sugar moiety after the ribose cycle is opened during oxidation. Mirzabekov do not teach any fragmentation. However, the fragmentation technique is taught by Morrow. Mirzabekov et al. disclose that the invention has considerable utility not only in the labeling of DNA, but also in the labeling of RNA molecules (See column 5, lines 29-31) and the phosphate group of the 3' terminal position on RNA can be easily removed with phosphatase before the following labeling procedure (See column 34-38).

For the reasons set forth above, Applicant's arguments filed 5/20/2003 have been fully considered but they are not persuasive. Thus, the rejection is maintained.

6. Claims 2, 21-22, 27-28, 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morrow (5,684,149) in view of Mirzabekov et al. (5,981,734) as applied to claims 1, 4-6, 8, 10-13, 19-20, 23-26 and 32-37 above, and further in view of Szostak et al. (5,688,670).

The teachings of Morrow and Mirzabekov et al. are set forth in section 5 above and Morrow and Mirzabekov et al. do not address (as recited in claim 2, 21, 27 and 30) that DNA or RNA comprises at least one thiophosphate nucleotide, however, the use of thiophosphate nucleotide was well known in the art to be useful as disclosed by Szostak et al.

Szostak et al. disclose thiophosphorylated RNA (See column 15, lines 41-43) as important for binding, catalysis or both (See column 16, lines 51-53) for creating, identifying and

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isolating catalytic RNA molecule. Therefore, the teachings of Szostak et al. would have motivated one of ordinary skill in the art at the time of the instant invention to use either DNA or RNA comprising at least one thiophosphate nucleotide in the method of Morrow to carry out the method as claimed. It would have been prima facie obvious to carry out the method as claimed.

The response argues that Szostak et al. do not teach chemically fragmenting DNA, RNA or chimeric DNA-RNA in the presence of multivalent metal cation, nor does it teach or suggest attaching a labeling agent at freed terminal phosphates located at the 3' end and/or 5' end. However, the claims do not have the purpose of using thiophosphate nucleotide in DNA fragmenting method. The argument does not commensurate the scope of the claims.

For the reasons set forth above, Applicant's arguments filed 5/20/2003 have been fully considered but they are not persuasive. Thus, the rejection is maintained.

7. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Morrow (5,684,149) in view of Mirzabekov et al. (5,981,734) as applied to claims 1, 4-6, 10-13, 19-20, 26 and 32 above, and further in view of Marliere et al. (5,407,797).

The teachings of Morrow and Mirzabekov et al. are set forth in section 5 above and Morrow and Mirzabekov et al. do not indicate physically separation of the labeled nucleic acid fragment from unattached labeling agent.

Marliere et al. disclose a hybridization probe for detecting the existence of bacteria in a sample (See the Abstract). The method of Marliere et al. involves the removal of unreacted

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molecules or fragments of molecules of probe on a support in which it can be carried out by washing with a buffer solution of suitable ionic strength (See column 8, lines 60-67).

One of ordinary skill in the art at the time of the instant invention would have been motivated to modify the method of Morrow by applying the teachings of Marliere et al. to separate the labeled nucleic acid fragment from unattached labeling agent as claimed with reasonable expectations of success because the method of Marliere et al involving this separation step is very specific for the bacteria. Thus, it would have been prima facie obvious to carry out the method as claimed.

The response argues that Marliere et al. do not teach chemically fragmenting DNA, RNA or chimeric DNA-RNA in the presence of multivalent metal cations, nor does it teach or suggest attaching a labeling agent at freed terminal phosphates located at the 3' end and/or 5' end. However, as discussed in section 5 above, the rejection over Morrow in view of Mirzabekov et al. is maintained. Marliere et al. disclose the removal of unreacted molecules or fragments of molecules of probe on a support in which it can be carried out by washing with a buffer solution of suitable ionic strength (See column 8, lines 60-67). The way of removal of unreacted molecules in the method of Marliere et al. is a type of physically separation. Therefore, Applicant's arguments filed 5/20/2003 have been fully considered but they are not persuasive. Thus, for the reasons set forth above, the rejection is maintained.

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8. Claims 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morrow (5,684,149) in view of Mirzabekov et al. (5,981,734) as applied to claims 1, 4-6, 10-13, 19-20, 23-26 and 32-37 above, and further in view of Stefano (6,297,010).

The teachings of Morrow and Mirzabekov et al. are set forth in section 5 above and Morrow and Mirzabekov et al. do not indicate betaine which is used in a buffer for the elution of the labeled nucleic acid.

Stefano discloses betaine which is used in the elution of the sample strand ligation product (See column 14, lines 34-47).

One of ordinary skill in the art at the time of the instant invention would have been motivated to modify the method of Morrow by applying the teachings of Stefano to elute the labeled nucleic acid fragment from a solid support because Stefano indicates that betaine reduces background and minimizes the effect of the base composition surrounding the locus may have on the thermal stability of the duplex and thus on the ability to detect a sequence change (See column 14, lines 34-47) and additionally, betaine can be used in room temperature for strand separation (See column 14, lines 34-47). It would have been prima facie obvious to carry out the method as claimed.

The response argues that Stefano fails to chemically fragmenting DNA, RNA or chimeric DNA-RNA in the presence of multivalent metal cations, nor does it teach or suggest attaching a labeling agent at freed terminal phosphates located at the 3' end and/or 5' end. However, as discussed in section 5 above, the rejection over Morrow in view of Mirzabekov et al. is

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maintained. The claim language does not require what is the purpose for using betaine in DNA or RNA fragmenting and labeling. Therefore, Applicant's arguments filed 5/20/2003 have been fully considered but they are not persuasive. Thus, for the reasons set forth above, the rejection is maintained.

Allowable Subject Matter

9. Claims 3, 9 and 16-18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. The following is a statement of reasons for the indication of allowable subject matter:

No prior art has been found teaching or suggesting the method of fragmenting and labeling DNA or RNA in an *in vitro* nucleic acid amplification mixture, and in a single reaction with treating step by adding a chelating agent to the mixture after the fragmenting and labeling steps.

Summary

11. No claims are allowable.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

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MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiries concerning this communication or earlier communications from the examiner should be directed to Joyce Tung whose telephone number is (703) 305-7112. The examiner can normally be reached on Monday-Friday from 8:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119 on Monday-Friday from 10:00 AM-6:00 PM.

Any inquiries of a general nature or relating to the status of this application should be directed to the Chemical/Matrix receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Art Unit 1637 via the PTO Fax Center located in Crystal

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Mall 1 using (703) 305-3014 or 308-4242. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Joyce Tung

August 1, 2003



**ETHAN WHISENANT
PRIMARY EXAMINER**